Chapter

Introductory Chapter: Beyond Risk Alleles - Invoking Cognitive Lesions in Top-Down Strategic Analysis

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1. Introduction

Improvements in medical care have significantly extended life expectancies, upwardly shifting demographic indicators of the elderly worldwide. Coupled with falling birth rates, however, the number of patients suffering cognitive deficits has also increased. World Health Organization projections, for example, indicate that by 2050, more than 20% will fall in this sector, with considerably higher percentages in developed nations, placing large numbers of individuals at risk [1]. Among the elderly the most prevalent neurodegenerative disease is Alzheimer's disease (AD) with a lifetime risk above 60 of 33% for males and 45% for females. Its growth rate is anticipated to exceed nearly 100% that of current levels in developed nations and more than 300% in Southeast Asian countries [2]. These increases in age-related diseases, moreover, add to an already significant burden from such prevalent mental health diseases as schizophrenia and bipolar disorder.

Symptomatically, prevalent diseases like AD and Korsakoff's syndrome, exhibit profound memory losses. In AD a broad consensus posits that its early symptoms include memory lapses that involve episodic memory, semantic recall, and visual orienting [3]. Among its earliest is an impaired sense of smell, a feature that may relate to evolutionary survival value. With the progression of AD, recent memories fade, and there is a proportionately greater retention of older ones, a characteristic observation termed Ribot's law.

Defined as a process of encoding, storing, and retrieving sensorial or mental information, memory dysfunctions induced by AD may be functionally interpreted as to the manner by which one or more of these phases are affected. Accordingly, the loss of formed memories, or retrograde amnesia, observed in AD patients, can be explained either by a loss of stored memories or an inability to retrieve them. In fact, existing evidence suggests that both phases are affected. Anatomical studies, for example, show a deterioration of thinly myelinated regions like the hippocampus relatively early in the disease progression compared to other regions [4]. Since the hippocampus is a critical center for recently formed memories, this evidence is consistent with loss of memories, particularly those that have formed first.

On the other hand, the disease is known to also specifically affect DMN operation [5], a domain thought to be critical to forming the self-construct. First identified by nuclear imaging studies that showed consistently higher levels of activity during passive task conditions, the DMN was hypothesized to monitor the external environment, body, and even emotions [6]. Task-related increases in activity in regional brain zones coincided with its decreased activity, indicating a reciprocal relation between the two zones related to the performance state of the

task. Functional MRI shows that these relative activity levels are substantially and progressively altered by Alzheimer's disease [7]. For example, in AD patients the posterior cingulate and right inferior temporal cortical activities decline, whereas the activity of the bilateral inferior parietal cortex increases. Because the zones form central connectivity hubs within the DMN, the activity changes appear to reflect a weakening of causally influential relations among its principal nuclei. Metastability indices for AD patients, for example, are reduced in decoupled, desynchronized states, revealing that the disease progression significantly reduces the brain's ability to entrain regional dynamical activity [8].

Unlike AD, on the other hand, Korsakoff's syndrome manifests as a persistent memory impairment that associates chiefly with the acquisition of new information [9–12]. Accordingly, it has been frequently classified as a disease yielding an anterograde form of amnesia. Like AD, on the other hand, its influence is multipronged, with studies showing that it also affects memory retrieval. Moreover, other studies show a preponderance of perifunctional influences rather than direct influences on episodic and semantic memory per se. For example, context memory, which makes an important contribution to memory recollection, has been shown to be significantly impaired in Korsakoff's patient. In memory tests, additionally, differential impairments are seen between AD and Korsakoff's disease and also Huntingdon's disease. For example, KS and HD patients performed considerably better than AD patients in recall memory [13].

The complexity of the influences of the two diseases on memory, notwithstanding, the distinctions in their manifestation suggest that these could be exploited both to resolve the likely etiological differences between the two and also to gain insight into underlying processes of memory and its relation to the self-construct. Differences in phenotypic manifestation, notably, have motivated much research, on the presupposition that they reflect the presence of different processes contributing to a single, albeit complex, function. Moreover, differences in manifestation also have bearing on therapeutic interventions and managed patient care, illustrated in the chapters of this edited volume.

Research into diseases like hemophilia has traditionally sought to resolve underlying etiopathological features by exploring genetic and biochemical differences that traced their manifestations to single, albeit critical, constituents of biochemical mechanisms, like the coagulation defects of Factor VIII in hemophiliac patients [14]. Cognitive diseases, on the other hand, are likely to differ greatly from those with such 'metabolite-like features due to the nervous systems's global role in integrating organismal function. Thus numerous aspects affected by these diseases are likely to differ, including their manner of functioning, composition, and hierarchy [15, 16]. Hence, there is the question of whether traditional strategies based on reductive approaches that attempt to determine etiology from genetic or molecular origins are an adequate beginning for investigating normal or disease-affected cognition. Indeed, the present volume illustrates both the challenge and the enigmatic character of such diseases. Accordingly, it is the intention of this introductory chapter to consider the limitations to study emerging from the adoption of such reductive strategies and the prospects of exploiting "higher-order differences" of the sort seen in AD and Korsakoff's disease, to infer etiopathological origins.

2. Approaching etiology through risk alleles

Clinically, the identification of risk alleles has significantly benefitted medical diagnosis and therapy. For example, diagnosis of the risk allele for hemophilia A, Factor VIII has high predictive power of, for example, likely hematoma when the hemophilia patient

is injured. Its utility, however, extends beyond risk prediction. Because mutant alleles usually constitute sources of malfunctioning protein products, genetic identification of the product can afford access to an otherwise enigmatic etiology. Studies of the Factor VIII allele have facilitated, for example, the determination of the disease's genetic basis, the role of the Factor VIII protein in clotting, and moleular therapeutic options [17].

The strategy of investigating etiology via risk alleles is a legacy of experimental designs that were successfully pursued for the elucidation of biochemical pathways. The presupposition behind these early, now classical approaches conceived of such pathways as linear sequences of progressively altered metabolite products, where each succeeding step entailed a molecular modification and the succession of steps yielded a unique biochemical product. Biochemical pathways fit this decidedly causal and prototypical model. The successive conversion of glucose to pyruvate in the glycolytic pathway, for example, evidenced the stepwise deconstruction by which the larger glucose molecule was gradually disassembled to the smaller pyruvate metabolite. Alleles controlled individual steps through their enzymatic products, which regulated each biochemical change. By rendering the protein products nonfunctional through techniques like mutagenesis given steps of the pathway could be arrested.

Such mutagenesis strategies achieved remarkable success in elucidating pathway steps due to the high specificity and mono-functionality of the enzymes regulating metabolite conversion. Mutation of the gene loci notably yielded focal and highly targeted effects that enabled the reconstruction of the entire pathway, when occurring within a linear sequence and involving a sufficient number of interruptions. By building on naturally occurring lesions, the development of reagents capable of modifying DNA rapidly expanded available tools for DNA dissection. With the advent of molecular biological procedures gene products could be altered at virtually any locus, allowing both pathway reconstruction and characterization of whole clusters of supramolecular assemblies [18].

The success of pathway reconstruction in metabolism led to the implementation of mutagenesis to dissect neural function in simple organisms amenable to genetic manipulation, like *C. elegans* and *Drosophila* on the presupposition that such simple functions were composed of similar molecular sequences; later applied for more complex neural functions like learning. This presupposition was consistent with the nearly universal cellular use of enzymatic catalysis to drive molecular and supramolecular events. It was consistent, moreover, with what was known of causally sequential events that occurred in neural operation, like the activation of synaptic vesicle release following the arrival of an action potential at a synapse. Hence, the use of the strategy extended apparently reasonable presuppositions about the construction of underlying processes to higher neural function.

The success of the mutagenesis strategy for elucidating biochemical pathways, which had motivated its use for exploring neural function, however, was due to a fortuitous confluence that juxtaposed the compositional nature of metabolism - with its linear and precise factory like assembly - with a causal conception involving successive influences effected via steplike sequences. Applied to neural function this conception analogized photopotential generation to a metabolite and the neural events of transduction to successive changes in a single molecular substance. Rather than metering the presence of a physical product, assessments were thus made in terms of the physiological feature, which was viewed as its conceptual equivalent.

Large-scale mutagenesis of fruit flies generated numerous "risk alleles" affecting various components of the photopotential, including its onset, maintenance, termination, and facilitation [19–22]. The strategy usefully characterized highly

penetrant alleles with Mendelian-like features, such as those affecting the photopigment protein, and physical components directly mediating the photopotential, like temperature-sensitive channel variants. However, while the strategy yielded numerous novel observations about photoreceptor function—including insight into mechanisms of prolonged potential activation, habituation-like responses, and degenerative cascades—the resolution of transduction per se was less easily and less well resolved. With hindsight and drawing from ongoing parallel studies of phototransduction that did not resort to genetic studies, the lack of resolution may now be partially traced to the conceptual equating of a physical component with a physiological function. Differences in the physical instantiation of a function - as opposed to a metabolite - became notably apparent with the discovery of features such as gated switching, nonlinear dynamical gain and the use of multicomponent protein complexes [23]. For example, generation of the photopotential is critically dependent on the asymmetric distribution of Na and K ions across the photoreceptor cell membrane. Yet, the ionic distribution is not itself generated by the transduction event but is an a priori condition that is required to successfully elicit the photopotential, one that must be maintained continuously against a concentration gradient by energy-consuming ionic pumps. A mutation rendering the pumps ineffective—for example, through a temperature-sensitive, cell mosaic line—would result in the absence of the photopotential and so be interpreted as affecting a step in the transduction pathway. Likewise, the photopotential amplitude displays gain adjustments that enable the detection of intensity variation under widely variant background illumination conditions affecting but not directly constituting the phototransduction events. These observations reveal that unlike the succession of steps occurring in metabolite processing the generation of the photopotential entails a coordinated operation of multiple independent functionalities that are each necessary but not sufficient for the potential to occur. Because each of these functionalities is potentially influenced by multiple alleles, the number of alleles affecting the transduction mechanism is likely to be much larger than that needed in a simple sequence of molecular alterations involving a single substance. In other words, the number of risk alleles that could affect the function is likely to be considerably more than the number of processional events needed to yield the function and indeed is likely to multiply that number. The magnitude of this multiplicative effect becomes especially significant when scaled for complex neural events. Accordingly, differences between the physical mechanisms of metabolism and those of photopotential generation require that the equating of neural function with metabolite processing be reconceived, a conceptual adjustment revealed through the findings of the mutagenesis approach.

3. Massive allelic effects in cognition

Phototransduction clearly constitutes a moderately complex but nonetheless basic function that has evolved to capture light information, in which multiple functionalities work together to yield the photopotential. As a neural mechanism, however, its level of complexity is arguably much less than many behavioral mechanisms operating at systemic and global scales. Motor execution and action identification, for example, require the involvement of visual pathways, task positive frontoparietal networks, premotor and motor cortices, and cerebellar circuits [24]. These are further complicated by the need to evoke egocentric frameworks in goal-directed actions. Consistent with these broad operational requirements, key risk alleles for major cognitive etiopathologies like schizophrenia—with a prevalence of 0.5–1%—are now known to include more than 120 significant loci, that is, alleles

that introduce statistically significant changes in manifest clinical symptoms [25]. Moreover, the rate of increase in their discovery has accelerated in recent years, not slowed. Classically, traits governed by large numbers of alleles yield only marginal and quantitative trait variation, with significant changes observed only in cases of rare alleles with high penetrance. Accordingly, many more difficult to detect alleles are likely to also contribute to the manifestation of the disease. In like manner, genetic studies of AD have also identified numerous risk alleles contributing to its etiopathology [26].

Together, the genetic studies show that cognitive diseases, as a group, are polygenic, often influencing hundreds of known alleles with perhaps a much greater unidentified number also influencing disease severity. Variation in behavioral effects due to any single allele, moreover, is small, with observed changes likely to be of a quantitative rather than a qualitative nature. Alone, the use of risk alleles as a strategical undertaking is therefore unlikely to offer significant insight into a causal etiology. The studies, rather, implicate large numbers of affected neurons and circuits, that is, effects likely to be mediated at systemic and even organismal levels of neural function. The range of investigations that have been undertaken over decades of exploration, in fact, from single allele variation to genome-wide investigations reveal that while genetic influences are clearly at work in cognition—such diseases typically display statistically significant familial effects—such influences are apparently mediated through a complex overarching matrix of constraints, one that bears little resemblance to a stepwise biochemical sequence, for which allele study and mutational analyses were first and successfully used.

4. Exploring strategic options in hierarchy

The massive number of affected alleles and the generally enigmatic character of cognitive diseases—more than 13 different, major hypotheses have been advanced to date to explain AD etiopathology—pose significant quandaries in the selection of research strategies, which clearly have as their ultimate objective whole rather than partial and ineffective therapeutic intervention. In light of these realities that seem linked to the extraordinarily complex scales of cognitive operation, the observations from mutagenesis strategies of intermediate-level phenomena like the photopotential offer a strong stimulus for moving beyond purely reductive options in the strategic analysis of cognitive disease etiology.

The recognition that functions often require supramolecular structures, for instance, has motivated the use of proteomics to characterize large-scale protein aggregates. This move would dispense with the lower-level allele studies and focus on how function emerges from clusters of interacting units. Such an approach also holds a promise for its access to the technical virtuosity acquired over decades in the use of translational technologies and analytical protein and peptide biochemistries. In principal virtually any protein segment can now be modified and analyzed to ascertain how such changes causally interact with other protein components to yield specific functions.

For example, the flagellar motor that propels bacterial motion is a well-characterized example of a large supramolecular aggregate consisting of more than seven distinct proteins activated during chemotaxis. Ligand-based stimuli, internal-based phosphorylation modifications, and enhanced protein-binding interactions are now all known events discerned through proteomic studies. These mechanical features are an important aspect of explaining the causal succession for the motor's function, identified in philosophy of science accounts as the "how" question in functional explanation [27]. The motor's performance, however, must also conform to an organizational, that is,

design, principle to be functional, which is to say that the explanation for the motor's function must include a dimension beyond that of the succession of internal events leading to functional output. This latter explanation, termed the "why" question, is significant for revealing that efficient causal interactions require the design principle as an a priori condition for their realization, hence, answers to the 'how' question represent only causal outcomes of organizational form.

This invocaton of design principle is significant for identifying the primary causal origin of a function. Rather than determined from below, the mechanistic steps emerge from a predetermined order that is critical for defining material composition and operation. Moreover, the elicited function—the motor's operation, for example—is framed within the context of global organismal need. Accordingly, the emergence of the function is fundamentally related to non-reductive, top-down effects that reflect two aspects of organismal operation; first, an organizational order that governs associations of larger-order complexes (e.g., evident in motifs and network analysis) and, second, a global requirement to satisfy organismal need, seen, for instance, in goal directed activity.

Conceiving of neural function from this higher-order perspective—i.e, dynamically oriented and not static as in the conception of metabolites—has implications for considering the primacy of causes eliciting neural organization—not chiefly through the structuring of its anatomical features, where it is built from the bottom up, but as a dynamic and functional order that has a purposeful orientation, which is determined from the top down.

5. Pursuing top-down strategy in autonomy and goal-directed behavior

Viewed from the dynamic aspect of function, the order of causal priority is reversed where the chief influences underlying organization and performance are systemic and teleological. Lesions of higher-order neural functions, like memory, appear thereby as dysfunctional properties of global representations. Risk alleles, in this reading, and similar reductive approaches can be expected to offer little insight into cognitive operation at the level of neural constructs likely to be impaired in cognitive diseases. Investigations into cognition, instead, seem better directed when exploring the operation of extended networks that function as components of larger systemic or even global operations. By extension, lesions that may fruitfully reveal aspects of large-scale operation are more likely to involve systemic effects that are more closely apposed to global processes mediating organismal tasking.

Models that define the source of this tasking, accordingly, are likely to be helpful for identifying the sorts of lesions that can be usefully exploited for cognitive study. Key features underwriting global cognition notably include those preserving existential independence and the integration of the organism as a whole, that is, those providing for autonomous existence [28]. Understood as a capacity, autonomy implicates dispositional qualities of self-recognition and self-directedness; that is, it invokes self-constructs that elicit higher order operations, which, accordingly, can be disrupted by cognitive disease. As one such higher order operation, for instance, memory is directly elicited by such self constructs in order to facilitate autonomy. Lesions of higher-order capacities like memory, which are evoked by global constructs, may thus be usefully exploited for their properties and manner of elicitation [29, 30].

Emerging from the global operation of the brain, constructs like the self are clearly extraordinarily complex and in many respects seem less tangible than material constituents of reductive and low-level functions. Nonetheless, their organismal reality is clearly evident in manifestations of behavioral activity. For example, the association between a representation of the whole individual by his body and its

physical realization in the neural activity of the brain, that is, as a global brain state, is consistently observed in varied perceptual realizations of the self. And in another example the failure of infants in the A not B task to move toward a goal where last seen is interpreted as a failure in motor planning due to maturational insufficiency in mechanisms needed to situate the motor plan that are associated with representing the self as the whole body [31]. These examples suggest that top down aproaches can offer strategic alternatives that more readily yield insight into global brain operations that are manifested at organismal scales.

Indeed, the modern concept of the neural representation of the self, for example, evoked in circumstances where the body is dynamically engaged in intentional actions, is an increasingly well-understood global operation that has emerged from several experimental legacies traced to the notion of the motor image [24]. The image is now known to involve a covert action undertaken only mentally and as a simulation of a non-executed action, with current evidence suggesting that there is a close correspondence between goal-directed information and self-representation [32]. Mechanisms that are likely to shape self-content can therefore be expected to include, for example, cells, circuits, or processes that bear desires and intentions of the author, which are likely to be contained in egocentric networks [33], and which encode agent specific content about an experience. These have been sited to specific domains of the hippocampus, such as the lateral entorhinal cortex where they appear to be influenced by memory recall [34] such as the lateral entorhinal cortex, and to the angular gyrus of the parietal cortex, a region that has been previously identified with self- and bodily representation. Indeed, goal-directed information contained in these networks can be expected to uniquely modify the self-representation by relating the individual to an intended terminus via information that is goal specific.

6. Reconsidering lesions: AD and KS in top-down strategic analysis

The promise of top-down analysis predicts that global organization is selectively impaired at intermediate and even higher levels of brain function, such as those now being investigated through the motor plan. Indeed, disturbances in the sense of self that mark schizophrenia, for example, in prodromal and acute stages, have led to the recognition of the loss of self as a core symptom [35] where both body ownershipa nd sense of agency are impacted [36]. Current evidence on how representational content of the self may be affected and how this may be linked to the body suggest, in fact, that it is mediated through the motor plan, which thereby offers a strategic investigative tool. Insight into the neural features that these results may implicate, for example, can be inferred from misattribution errors that are experimentally evoked in normal individuals and that appear to be pathologically exacerbated in schizophrenic individuals [37].

By extension, memory losses in AD and KS are in their broad features consistent with functional losses that have organismal bearing and that can be revealed through such top-down analysis. Accordingly, this volume represents an effort to forward an argument for global strategies that can be pursued in cognitive etiopathologies. It is a proposal that emerges from the intractability of reductive study faced with the incredible complexity of operation that is intrinsic to cognition. While lacking in the tangible manifestations that have come to mark genetic and molecular study, the reality of global operation is nonetheless manifestly evident. Moreover, it is a reality for which new investigative tools are emerging from research studies, such as the motor plan. Revelation of distinct functional differences in memory loss in diseases like AD and KS, therefore, can be expected to further options for global, top-down study.

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